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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,760	06/22/2000	Martha K. Newell	10277/7009 HCL	8006

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/07/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

F 10

Office Action Summary

Application No.	Applicant(s)
09/599,760	Newell, M.
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 16, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-62, 65, 66, and 68-74* is/are pending in the application.

4a) Of the above, claim(s) *1-59, 65, 73, and 74* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *60-62, 66, and 68-72* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). 20
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed July 16, 2003, Paper No. 18.

Claims 1-62, 65, 66, 68-74 are pending in the instant application.

Election/Restriction

This application contains claims 1-59, 65, 73 and 74, drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Any rejections repeated in this Office action are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments with respect to rejection of claims 66 and 68-72 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention over the scope claimed, have been considered but are moot in view of the new ground(s) of rejection set forth below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66 and 68-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treating an infectious disease in an organism comprising the administration of a lysosomal targeted binding peptide UCP inhibitor or a lysosomal targeted binding molecule UCP inhibitor.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention claimed.

The state of the prior art and the predictability or unpredictability of the art. Bouillaud et al teach the expression of uncoupling protein (UCP) in brown adipose tissue, where UCP is known to uncouple mitochondrial respiration from ATP production by the introduction of a proton conducting pathway through the mitochondrial inner membrane. Bouillard et al teach the generation of dominant negative mutants of UCP upon the mutation of amino acids which are essential for nucleotide inhibition of the proton transport in UCP (See especially the abstract, introduction and figure 7). Cone teaches the general motivation of uncoupling oxidative phosphorylation from ATP production in cancer cells in order to reduce the proliferative capacity of such tumor cells (See especially columns 2-5). Szoka et al teach the lysosomotrophic

properties of weak bases such as chloroquine, monensin and PAMAM dendrimers in attempts to design polynucleotide delivery systems in combination with charge neutralization, membrane permeabilization and subcellular localization agents, which agents include lysosomal targeting agents (See especially abstract and columns 17, 18, 35 and 36). While the references cited above generally teach that the ability to alter the pH of lysosomes is routinely accomplished in the art, the ability to predictably and selectively target uncoupling or lysosomotrophic agents (such as those described by Bouillard et al, Cone, or Szoka et al) to appropriate target cells whereby treatment effects are provided in an organism, is currently not a routine matter in the art.

In addressing the general unpredictability regarding in vivo treatment efficacy with regard to target cell delivery and uptake limitations, Branch and Crooke teach that the in vivo (whole organism) application of therapeutic molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* capabilities of therapeutic molecules. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of therapeutic efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical

determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Cellular uptake of therapeutic molecules by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of therapeutic molecules in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating an infectious disease comprising the administration of a lysosomal UCP inhibitor. The specification teaches a shift in the expression of UCP from lysosomes and the mitochondria to the plasma membrane in MDR cells in vitro. The specification also teaches the induction of MDR cell death in vitro comprising the administration of tunicamycin and anti-UCP antibodies. The specification fails to teach the treatment of an infectious disease comprising the administration of a lysosomal targeted binding peptide UCP inhibitor or a lysosomal targeted binding molecule UCP inhibitor in an organism. One skilled in the art would not accept on its face the examples given in the specification of the changes observed in subcellular expression of UCP in cells in vitro following the administration of

tunicamycin, or the ability of UCP2 knockout mice to maintain resistance to T. Gondii infection, as being correlative or representative of the successful treatment of infectious diseases following the administration of lysosomal targeted binding peptide UCP inhibitors or lysosomal targeted binding molecule UCP inhibitors in an organism, in view of the lack of guidance in the specification and known unpredictability associated with the ability to target appropriate cells in an organism with UCP inhibitors, whereby cellular targeting and inhibitor uptake are obtained and treatment effects are provided. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with the *in vivo* delivery of UCP inhibitors and treatment effects provided by the administration of such inhibitors to an organism, and specifically regarding the instant compositions and methods claimed, which treatment methods are provided for infectious diseases or conditions comprising the administration by any route of lysosomal targeted binding peptide UCP inhibitors or lysosomal targeted binding molecule UCP inhibitors.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to a method for treating infectious diseases in any organism comprising the administration of lysosomal targeted binding peptide UCP inhibitors or lysosomal targeted binding molecule UCP inhibitors. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring lysosomal UCP activity, such that lysosomal pH is sufficiently

altered in appropriate target cells in vivo upon the administration of lysosomal targeted binding peptide UCP inhibitors or lysosomal targeted binding molecule UCP inhibitors, and further that treatment effects are provided for infectious diseases in an organism. Since the specification fails to provide any particular guidance for the targeting and cellular delivery of lysosomal targeted binding peptide UCP inhibitors or lysosomal targeted binding molecule UCP inhibitors in vivo whereby treatment effects are provided in an organism, and since determination of these factors for a particular UCP inhibitor is highly unpredictable for a particular target cell in vivo, it would require undue experimentation to practice the invention.

The findings observed that UCP2 knockout mice have increased resistance to infection to Toxoplasma gondii, and that UCP inhibitors were found to regulate lysosomal pH in vitro, are not representative of the ability to treat infectious diseases in an organism comprising the administration of any lysosomal UCP inhibitor. The generation of knock-out mice is not representative of the successful targeting and delivery of any lysosomal UCP inhibitors in an organism, whereby treatment effects have been provided. Knock-out mice are representative of a phenotype correlated with the ablation of a gene, but not representative of successful delivery and treatment comprising the administration by any route of any UCP inhibitor in an organism. It would require undue experimentation to determine formulations for the successful delivery of lysosomal UCP inhibitors in an organism, whereby treatment effects are provided.

Maintained Rejections

Claims 60-62, 66 and 68-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the Office action mailed January 14, 2003, Paper No. 17.

No arguments have been made addressing this rejection.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the

patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

October 5, 2003